PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 July 2000 (21.07.00)	
International application No. PCT/EP99/09002	**Applicant's or agent's file reference** SCB 518 PCT
International filing date (day/month/year) 23 November 1999 (23.11.99)	**Priority date** (day/month/year) 25 November 1998 (25.11.98)
Applicant LEWIS, David et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 June 2000 (09.06.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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MI99A001712	30 July 1999 (30.07.99)	IT

(71) Applicant *(for all designated States except US)*: CHIESI FARMACEUTICI S.P.A. [IT/IT]; Via Palermo, 26/A, I–43100 Parma (IT).

(72) Inventors; and

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(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PRESSURISED METERED DOSE INHALERS (MDI)

(57) Abstract

The invention relates to the use of pressurised metered dose inhalers (MDIs) having part or all of their internal surfaces consisting of stainless steel, anodised aluminium or lined with an inert organic coating; and to compositions to be delivered with said MDIs.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SCB 518 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 09002	23/11/1999	25/11/1998
Applicant		
CHIESI FARMACEUTICI S.P.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/09002

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 96 32099 A (GLAXO WELLCOME) 17 October 1996 (1996-10-17) claims 1,2,4,13,15,16 page 4, line 1 - line 33 page 5, line 6 - line 28 page 6, line 5 - line 8 page 6, line 21 - line 27	1-3,5-8, 10 4,9
X	WO 95 17195 A (MINNESOTA MINING AND MANUFACTURING COMPANY) 29 June 1995 (1995-06-29) cited in the application claims 1-4,18-20 page 18; example 29	1-3,5,6, 9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2000	29/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 642 992 A (CIBA-GEIGY) 15 March 1995 (1995-03-15) claim 1 column 4, line 50 - line 54 column 5, line 17 - line 18	1,6
Y	WO 98 24420 A (BIOGLAN IRELAND) 11 June 1998 (1998-06-11) claims 1-4,8,9,12,17	4
Y	WO 92 11236 A (SMITHKLINE BEECHAM) 9 July 1992 (1992-07-09) page 11; example 5	9
A	US 4 835 145 A (PETER MAC DONALD) 30 May 1989 (1989-05-30) column 2, line 13 - line 45 column 4; examples A,B	11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/09002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632099 A	17-10-1996	AU 710382 B	16-09-1999
		AU 5480996 A	30-10-1996
		BG 102021 A	31-07-1998
		BR 9604976 A	09-06-1998
		CA 2217950 A	17-10-1996
		CN 1186430 A	01-07-1998
		CZ 9703259 A	18-03-1998
		EP 0820279 A	28-01-1998
		HU 9801526 A	28-10-1998
		JP 11509433 T	24-08-1999
		NO 974737 A	11-12-1997
		NZ 306278 A	29-07-1999
		PL 322778 A	16-02-1998
		SK 138897 A	06-05-1998
WO 9517195 A	29-06-1995	AU 680967 B	14-08-1997
		AU 1098695 A	10-07-1995
		CA 2178473 A	29-06-1995
		EP 0735884 A	09-10-1996
		JP 9506896 T	08-07-1997
		NO 962585 A	18-06-1996
		NZ 276637 A	27-07-1997
		US 5980867 A	09-11-1999
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EP 642992 A	15-03-1995	AT 163623 T	15-03-1998
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		DE 59405357 D	09-04-1998
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		EP 0563048 A	06-10-1993
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		ZA 9107468 A	30-12-1992
US 4835145 A	30-05-1989	IT 1196142 B	10-11-1988
		AT 56725 T	15-10-1990
		CA 1336513 A	01-08-1995
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		EP 0164636 A	18-12-1985
		ES 543499 D	01-05-1987
		ES 8705462 A	16-07-1987
		FI 852093 A,B,	12-12-1985
		JP 1588637 C	19-11-1990
		JP 2013680 B	04-04-1990
		JP 61040299 A	26-02-1986
		NO 852327 A,B,	12-12-1985

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/09002

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4835145 A		US 4695625 A	22-09-1987

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB 518 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/09002	23/11/1999	25/11/1998
International Patent Classification (IPC) or national classification and IPC A61K9/00		
Applicant CHIESI FARMACEUTICI S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/06/2000	22.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rauter, A Telephone No. +49 89 2399 8645

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/09002

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-27	as originally filed

Claims, No.:

1-10	as received on	27/12/2000	with letter of	20/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10
	No:	Claims	1 - 9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1 - 10
Industrial applicability (IA)	Yes:	Claims	1 - 10
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION V. .....

1. Reference is made to the following documents:

   D1: WO-A-9 632 099
   D2: WO-A-9 517 195
   D3: EP-A-0 642 992
   D4: WO-A-9 824 420
   D5: WO-A-9 211 236
   D6: US-A-4 835 145

2. The present application does not satisfy the criterion set forth in Article 33(2) and (3) PCT because the subject-matter of independent claims 1 and 9 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT) and that of independent claim 10 does not involve an inventive step (Rule 65(1) and (2) PCT).

   The subject-matter of independent claim 1 relates to a dose inhaler comprising usual inhaler components, ie an active ingredient, a hydrofluorocarbon propellant and a co-solvent, and which inhaler is characterized in that part or all of the internal surfaces consist of stainless steel, anodised aluminium or are covered with an inert organic coating and which coating is to be selected from perflouroalkoxyalkane, epoxy phenol resin or flourinated-ethylene-propylene polyether sulfone. There is no possibility to consider functional features for novelty evaluations of product claims, like that of "said material preventing the chemical degradation of the active ingredient". Claim 9 relates to the solution formulation used in the inhaler of claim 1.

   Such products have already been disclosed in *eg* document D1. According to D1 a dose inhaler has been disclosed which comprises a solution of an active ingredient (see *eg* claim 1), a hydrofluorocarbon propellant (see *eg* claim 1; page 5, lines 7 - 17) and a co-solvent (see *eg* claim 4), and the internal surfaces are coated partly or completely by a presently comprised fluorocarbon polymer (see *eg* claims 17 - 19; page 6, line 21 - page 8, line 7) or by *eg* stainless steel (see *eg* page 6, lines 5 - 7).

The applicant argued during the international preliminary examination procedure that D1 and D3 refer only to "suspensions" and not to "solutions", however, the definition of the components intended to be comprised according to the wording of present claims 1 and 9 (see present description) by the term "solution" are not different to those comprised by "inhalation drug formulation" in D1, or "Suspension" in D3, and thus no difference in that respect can be seen.

Taking into consideration the wordings of claims 1 and 9, further novelty destroying disclosure is available from:
D2: see *eg* claims 1, 19 and 20 in particular when combined with the page 7, lines 13 - 17;
(During the international preliminary examination procedure the applicant argued and referred in particular to differencies with regard to D2 and present case, however, the arguments are not reflected, *ie* they found no expression in the wording of the presently claimed subject-matter, and must thus be disregarded.)
D3: see *eg* the claims; column 4, line 50 - column 5, line 16;

Dependent claims 2 - 8 are likewise not new since the specifically cited prior art comprises presently specified actives, the propellants or the other specified components.

The subject-matter of claim 10 relates to an aerosol formulation comprising dexbudesonide, a hydrofluorocarbon propellant, ethanol and a certain volatility compound.

According to D1 already aerosol formulations have been disclosed which differ from the present one only in that *dex*budesonide as the active has not been mentioned. However, the use of corticosteroids like budesonide (D1, see page 4, line 19) and epimers (see in particular D6) thereof are well known to be used in aerosols (see the example (a) in column 4 of D6) and a corresponding replacement of the active in the formulations of D1 must be regarded obvious to the person skilled in the art.

SECTION VII. .....

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3 - D6 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII. .....

1. The "solution" used in the inhaler, ie subject-matter of claims 1 and 9 on the one hand (dose inhaler/solution formulation) and the "solution formulation" of claim 10 on the other hand (aerosol) are characterised by different essential features. It appears at present that the international application does not relate to one invention only, since a single new general inventive concept is lacking (Rule 13 PCT).

CLAIMS

1. Pressurised metered dose inhalers containing a solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterised in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating selected from perfluoroalkoxyalkane, epoxy-phenol resin or fluorinated-ethylene-propylene polyether sulfone, said material preventing the chemical degradation of the active ingredient.

2. Pressurized metered dose inhalers according to claim 1, wherein the active ingredients are selected from ß2 agonists, steroids or anti-cholinergic agents and their combinations.

3. Pressurized metered dose inhalers according to claim 2, wherein the active ingredient is ipratropium bromide, oxitropium bromide, tiotropium bromide, flunisolide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, budesonide, ciclesonide, rofleponide and epimers thereof.

4. Pressurized metered dose inhalers according to any of claims from 1 to 3, containing a low-volatility component selected from glycerol,

polyethylene glycol and isopropyl myristate.

5. Pressurized metered dose inhalers according to any of claims from 1 to 4, wherein the co-solvent is ethanol.

6. Pressurized metered dose inhalers according to any of claims from 1 to 5, wherein the propellant is selected from HFA 227, HFA 134a and their mixtures.

7. Pressurised metered dose inhalers according to any of claims 1 to 6 wherein part or all of the internal surfaces are coated with an epoxy phenol resin.

8. Pressurised metered dose inhalers according to any of claims 1 to 5 wherein part or all of the internal surfaces consist of anodised aluminium.

9. Stabilized aerosol solution formulation consisting of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component for use in a pressurised metered dose inhaler as claimed in any of claims 1 to 8.

10. Aerosol solution formulation of dexbudesonide in a hydrofluorocarbon propellant and ethanol as a co-solvent, further comprising a low volatility compound selected from glycerol, isopropylmyristate and polyethylene glycol.

CLAIMS

1. Pressurised metered dose inhalers containing a solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterised in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating.

2. Pressurized metered dose inhalers according to claim 1, wherein the active ingredients are selected from ß2 agonists, steroids or anti-cholinergic agents and their combinations.

3. Pressurized metered dose inhalers according to claim 2, wherein the active ingredient is ipratropium bromide, oxitropium bromide, tiotropium bromide, flunisolide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, budesonide, ciclesonide, rofleponide and epimers thereof.

4. Pressurized metered dose inhalers according to any of claims from 1 to 3, containing a low-volatility component selected from glycerol, polyethylene glycol and isopropyl myristate.

5. Pressurized metered dose inhalers according to any of claims from 1 to 4, wherein the co-solvent is ethanol.

6. Pressurized metered dose inhalers according to

any of claims from 1 to 5, wherein the propellant is selected from HFA 227, HFA 134a and their mixtures.

7. Pressurised metered dose inhalers according to any of claims 1 to 6 wherein the inert organic coating is perfluoroalkoxyalkane, epoxy-phenol resin or fluorinated-ethylene-propylene polyether sulfone.

8. Pressurised metered dose inhalers according to any of claims 1 to 7 wherein part or all of the internal surfaces are coated with an epoxy phenol resin.

9. Pressurised metered dose inhalers according to any of claims 1 to 6 wherein part or all of the internal surfaces consist of anodised aluminium.

10. Stabilized aerosol solution formulation consisting of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component for use in a pressurised metered dose inhaler as claimed in any of claims 1 to 9.

11. Aerosol solution formulation of dexbudesonide in a hydrofluorocarbon propellant and ethanol as a co-solvent, further comprising a low volatility compound selected from glycerol, isopropylmyristate and polyethylene glicol.